Amyloid and Amyloidosis

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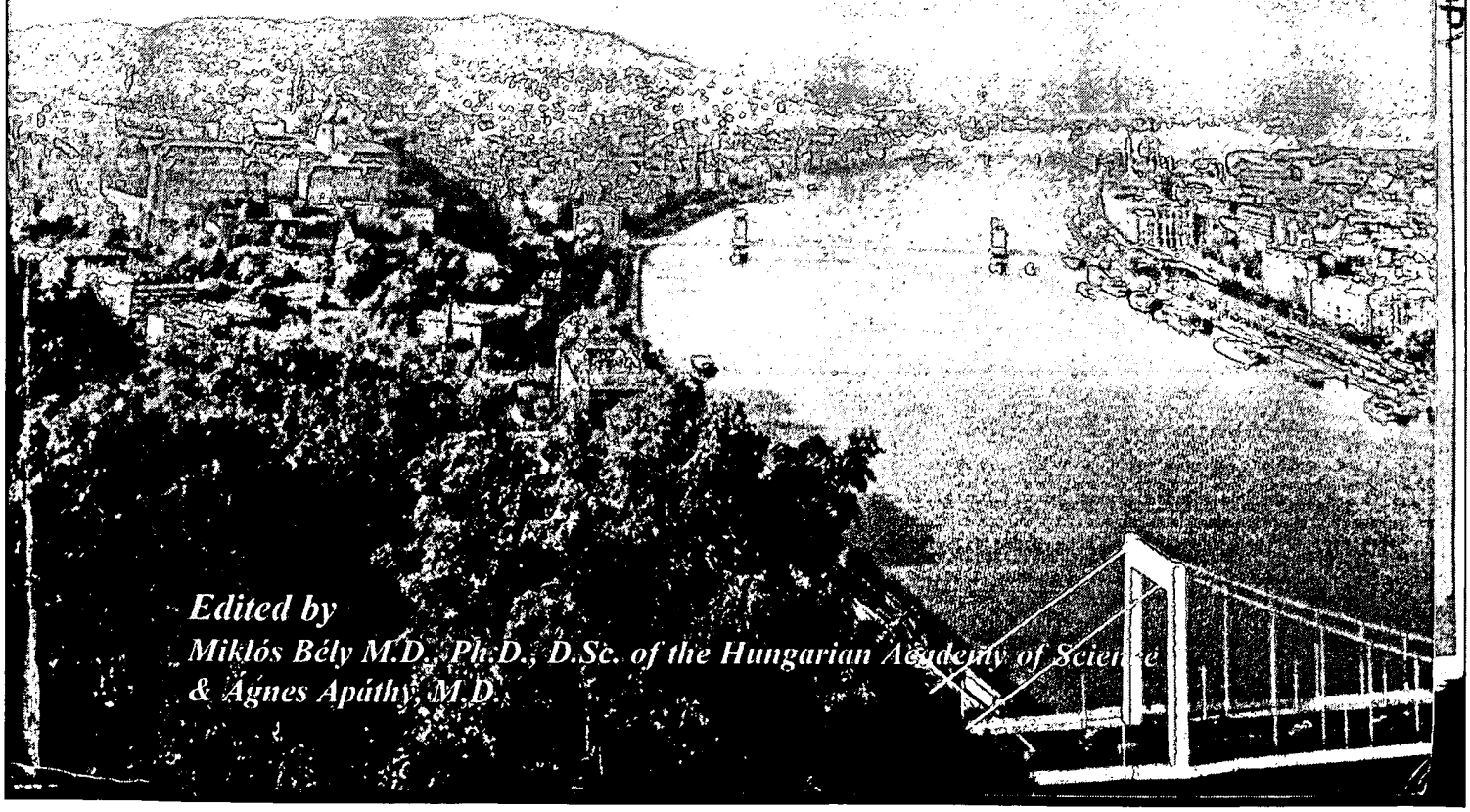

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VACCINE BASED THERAPY FOR PRIMARY (AL) AMYLOIDOSIS

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Introduction: Therapeutic efforts in patients with AL amyloidosis have been directed primarily toward reducing the synthesis of the amyloid light chain precursor through conventional or high-dose chemotherapy. Although there have been reports that the latter treatment may lead to regression of amyloid deposits, this approach is limited to a select group of patients and can be associated with significant morbidity. It was observed that certain patients treated with the iodinated anthracycline IDOX had reduction in amyloid burden; however, this agent is apparently only of limited benefit and, with rare exception, does not affect systemic deposits. We have reported that mice injected with human AL extracts develop polyclonal antibodies that react not only with the amyloid injected but also recognize heterologous deposits regardless of their subgroup or isotype; further, when such mice were re-injected with the same (or other) AL amyloid extracts, the rate of amyloidolysis was greatly accelerated[1]. Based on our results obtained in our experimental *in vivo* amyloidoma model, it has become apparent that such deposits can be removed by an immune-mediated mechanism that involves the administration of mAbs having reactivity for an amyloid–related epitope. These observations have now led us to studies involving immunization of mice with synthetic AL-related fibrils in order to determine if this form of "active" immunotherapy could be used in patients with AL amyloidosis.

Materials and Methods: The protein used for immunization was a human recombinant rVλ6 molecule that was converted into fibrils as a result of thermal agitation. Groups of 6-wk old Balb/c mice were immunized with a series of 3 weekly *i.p.* injections of alum-suspended fibrils (0.1 mg/ml), followed by boosts at wks 6 and 8. Sera of control (alum only) and immunized mice were tested for anti-fibril reactivity by ELISA and immunohistochemically against AL amyloid fibrils and tissue deposits, respectively. On wk 9, both sets of mice were injected *s.c.* with up to 100 mg of human ALλ or ALκ extracts prepared by the standard water isolation procedure of Pras et al[2]. This material was injected between the scapulae, forming a readily palpable tumor, i.e., an amyloidoma. The rate of disappearance of the resultant amyloidomas was measured daily by palpation.

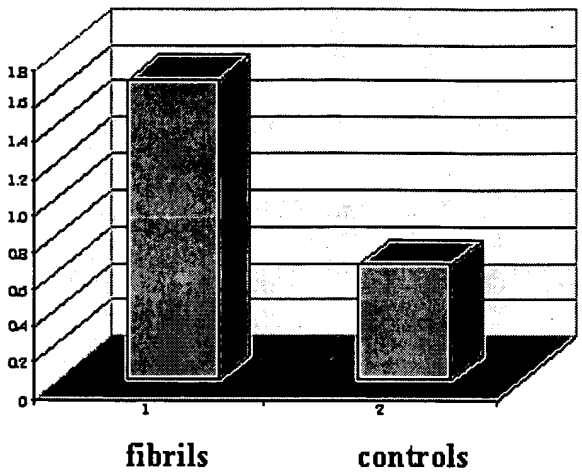

Figure 1. Comparison of serum anti-fibril reactivity in immunized (fibrils) and control mice

immunohistochemically against ALκ and ALλ deposits. When ALκ or ALλ amyloidomas were induced, those mice that mounted an immune response to the vaccine eliminated the material at a 2- to 3-fold more rapid rate than the control animals or those that did not develop a significant antibody response (Fig. 2).

Results: With rare exception, all mice immunized with the synthetic fibrils had readily detectable serum anti-amyloid antibodies that recognized not only the immunogen, but also heterologous AL fibrils regardless of their subgroup or isotype (Fig. 1). The same type of reactivity was confirmed

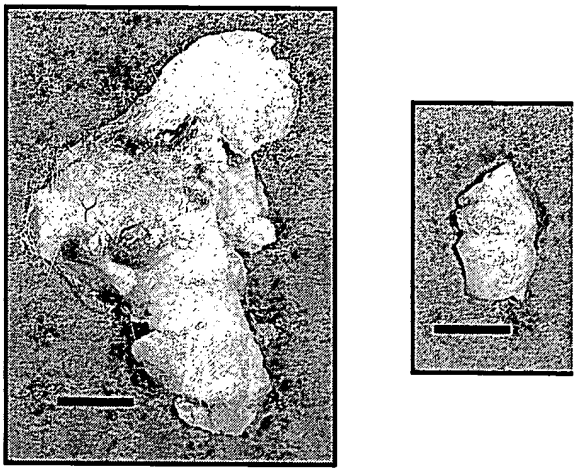

Figure 2. Resolution of AL amyloid tumors in immunized (right) and control mice (left). The amyloidomas were excised 4 post-injection. Bars = 5 mm.

Conclusion: The use of synthetic light chain fibrils as an anti-amyloid vaccine has been found to accelerate AL amyloidolysis. Our experimental results suggest that this could provide a novel means to treat patients with primary (AL) or other forms of systemic amyloidosis. The development of passive or active anti-amyloid therapeutic strategies in order to reduce amyloid burden and improve organ function would represent a major advance not just for AL patients, as well for those with other acquired or inherited amyloid-associated disorders.

References:

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2. Pras, M., Schubert, M., Zucker-Franklin, D., Ramon, A. and Franklin, E.C. (1968) The characterization of soluble amyloid prepared in water. *J. Clin., Invest.,* **47**, 924-933

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